II. REMARKS

Formal Matters

Claims 1-14 and 18-20 are pending after entry of the amendments set forth herein.

Claims 1-11 and 16-19 were examined and were rejected. Claims 12-14 were withdrawn from consideration.

Claims 1-11, 18, and 19 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claim 1 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 17, lines 12-22; and page 18, lines 10-24. Accordingly, no new matter is added by the amendments to claim 1. No new matter is added by the amendments to claims 2-11, 18, and 19.

Claims 16 and 17 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 20 is added. Support for new claim 20 is found in claim 3 as originally filed, and throughout the specification, including the following exemplary location: page 2, lines 24-25. Accordingly, no new matter is added by new claim 20.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-11 and 16-19 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite

The Office Action stated that claims 1-11 and 16-19 are vague and indefinite for the recitation of Ser(*P*); and recommended amending the claims to recite "wherein amino acid residue X of SEQ ID NO:1 is a phosphoseryl residue."

Claims 1, 3, and 4 are amended to recite "X" instead of "Ser(*P*)" and to recite "wherein amino acid residue X of SEQ ID NO:1 is a phosphoseryl residue," as recommended in the Office Action.

Conclusion as to the rejection under 35 U.S.C. §112, second paragraph

Applicants submit that the rejection of claims 1-11 and 16-19 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-11 and 16-19 were rejected under35 U.S.C. §112, first paragraph, as allegedly failing to comply

with the enablement requirement. Claims 1-11 and 16-19 were rejected under35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Enablement

The Office Action stated that the instant claims recite a peptide comprising a recited amino acid sequence "and conservative substitutions therein"; and stated that the specification fails to teach any conservative substitution that can be made in any of the recited sequences while still maintaining antimicrobial activity.

Without conceding as to the correctness of this rejection, claims 1 and 4 are amended to delete "and conservative substitutions therein."

Written description

The Office Action stated that the instant claims recite a peptide comprising a recited amino acid sequence "and conservative substitutions therein"; and stated that the specification fails to provide written description for variants that maintain antimicrobial activity.

Without conceding as to the correctness of this rejection, claims 1 and 4 are amended to delete "and conservative substitutions therein."

Conclusion as to the rejections under 35 U.S.C. §112, first paragraph

Applicants submit that the above-discussed rejections under 35 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

Rejection under 35 U.S.C. §102(b)

Claims 1-4 were rejected as allegedly anticipated by Reynolds et al. (WO 99/26971; "Reynolds").

The Office Action stated that Reynolds teaches non-glycosylated peptides comprising SEQ ID NOs:1-70 having less than about 100 or 70 amino acids; and stated that the composition taught by Reynolds may comprise magnesium stearate. Applicants respectfully traverse the rejection.

Claim 1 as amended recites that the divalent cation is a Ca^{2+} or a Zn^{2+} ion. Reynolds neither discloses nor suggests an antimicrobial composition as recited in claim 1, wherein the divalent cation is a Ca^{2+} or a Zn^{2+} ion. As such, Reynolds cannot anticipate any of claims 1-4.

Conclusion as to the rejection under 35 U.S.C. §102(b)

Applicants submit that the rejection of claims 1-4 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §103(a)

Claims 1-11 and 16-19 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Reynolds in view of Cummins et al. ((1991) *J. Clin. Periodontol.* 18:455; "Cummins") and Phan et al. ((2004) *Oral Microbiol. Immunol.* 19:31; "Phan").

The Office Action stated:

1) Reynolds teaches non-glycosylated peptides comprising SEQ ID NOs:1-70 having less than about 100 or 70 amino acids;
2) Reynolds teaches the use of these peptides for antimicrobial compositions for treatment of caries or periodontal disease;
3) Reynolds does not specifically teach the use of the divalent cations Zn^{2+}, Ca^{2+}, etc.;
4) Cummins teaches that the divalent metal ion zinc reduces growth and metabolism of oral bacteria by interacting with sulfhydryl groups on bacterial enzymes, inhibiting their activity;
5) Phan teaches that zinc is largely bacteriostatic, although very high concentrations have a bactericidal effect; and
6) Phan teaches that zinc can inhibit acid an alkali production by oral streptococci in suspensions and biofilms.

The Office Action concluded that it would have been obvious to include the divalent cation Zn^{2+} in the compositions comprising the antimicrobial peptides taught by Reynolds "because Reynolds specifically teach the use of their peptides for treatment of caries or periodontal disease and both Phan and Cummins teach the antibacterial properties of zinc against oral bacteria." Office Action, page 12. Applicants respectfully traverse the rejection.

The law regarding obviousness

In order to meet its burden in establishing a rejection under 35 U.S.C. §103(a), the Patent Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. MPEP § 2143(A). In addition to demonstrating that all elements were known in the prior art, the Patent Office must also articulate a reason for combining the elements. *See, e.g., KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct 1727 (2007) ("*KSR*") at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.,* 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*; and *Innogenetics, N.V. v. Abbott Laboratories* 512 F.3d 1363, 1373, 85 USPQ2d 1641 (Fed. Cir. 2008). A generalized

motivation to develop a method is not the kind of motivation required by the patent laws.[1]

In *KSR*, the Supreme Court reviewed the teaching-suggestion-motivation (TSM) test. Subsequently, the Federal Circuit reiterated the value of the TSM test, stating that a flexible TSM test remains the "primary guarantor against a non-statutory hindsight analysis."[2] Indeed, the Court reiterated the importance of identifying "a reason that would have prompted a person of ordinary skilled in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination.[3]

Evidence that supports a finding of non-obviousness includes teaching away, unexpected results, skepticism of others in the field, copying, long-felt but unsolved need, and commercial success.[4] Such evidence must be considered before a conclusion of obviousness is reached.[5] Such evidence is not just a cumulative or confirmatory part of the obviousness calculus, but constitutes independent evidence of non-obviousness,[6] or, as stated in *Hybritech*, consideration of such evidence is not merely "icing on the cake."[7] The concept that teaching away is one of the indicia of non-obviousness is well established. In *United States v. Adams,* 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966); and *Crocs, Inc. v. U.S. Int'l Trade Comm'n*., 598 F.3d 1294 (Fed. Cir. 2010).

There is no motivation in the cited art to combine the references.

As discussed in detail below, the cited art does not provide any motivation to combine the reference teachings, or to make the Office Action's proposed modification of Reynolds.

Reynolds

Reynolds does not provide any motivation to combine the cited references, or to make the proposed modification. Indeed, Reynolds asserts that the peptides disclosed therein exhibit anti-microbial activity, and does not describe any deficiencies in the anti-microbial activity of the peptides that would motivate a person to include zinc in a composition comprising such peptides.

Even if a person skilled in the art were to be motivated to modify the peptides discussed in Reynolds, and

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[1] *Innogenetics, N.V. v. Abbott Laboratories* 512 F.3d 1363, 1373, 85 USPQ2d 1641 (Fed. Cir. 2008)
[2] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc.* 520 F.3d 1358, 1364, 86 USPQ2d 1996 (Fed. Cir. 2008)
[3] *Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc. v. Alphapharm Pty., Ltd. and Genpharm, Inc.* 492 F.3d 1350, 1357, 83 USPQ2d 1169 (Fed. Cir. 2007)
[4] *Graham* 383 U.S. at 17 (1996)
[5] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986)
[6] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc.* 520 F.3d 1358, 1365, 86 USPQ2d 1996 (Fed. Cir. 2008)
[7] *Hybritech* 802 F.2d at 1380

it is Applicants' position that the cited art does not provide any such motivation, such a person would have been presented with a number of options, and would not necessarily have chosen zinc as the option.

Phan

Phan actually discloses that zinc has poor anti-microbial activity. Phan states on page 36, third column, that Zn^{2+} alone "did not appear to be bactericidal for oral streptococci even at levels of 20 mM as the sulfate or chloride salts"; and states that the bactericidal effect of zinc citrate in biofilms was "minimal." Phan further states:

> "The nature of the lethal effect is not clear, but it requires zinc levels higher than those for the other inhibitory actions described here and probably higher than those achievable in biofilms in the human mouth."

Phan, page 36, third column under "Zinc killing."

Phan thus does not provide any motivation to combine zinc with a peptide as recited in the instant claims.

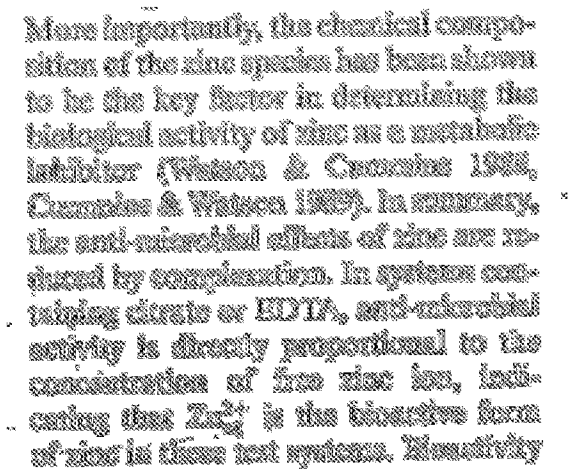
Cummins

Cummins also does not provide any motivation to combine the reference teachings, or to make the Office Action's proposed modification of Reynolds. Indeed, as discussed below, Cummins teaches away from the proposed modification.

Cummins teaches away from the proposed modification.

Cummins teaches away from the Office Action's proposed modification, i.e., Cummins teaches away from including the divalent cation Zn^{2+} in the compositions comprising the antimicrobial peptides taught by Reynolds.

In Cummins, it is noted on page 457, center column that:


More importantly, the chemical composition of the zinc species has been shown to be the key factor in determining the biological activity of zinc as a metabolic inhibitor (Watson & Cummins 1978, Cummins & Watson 1979). In summary, the anti-microbial effects of zinc are reduced by complexation. In systems containing citrate or EDTA, anti-microbial activity is directly proportional to the concentration of free zinc ion, indicating that Zn^{2+} is the bioactive form of zinc in these test systems. Reactivity

It should be emphasized that, in the above-noted passage, Cummins states that "**the anti-microbial**

effects are reduced by complexation." Thus, the above-noted passage teaches a person skilled in the art that zinc, when complexed to another component, **has reduced anti-microbial effects**. As such, Cummins teaches away from the Office Action's proposed modification, i.e., Cummins teaches away from including the divalent cation Zn^{2+} in the compositions comprising the antimicrobial peptides taught by Reynolds.

The state of the art relating to certain peptides discussed in Reynolds is outlined in the background section of the present application. The peptides discussed in Reynolds are referred to as Kappacin, or variants thereof. Kappacin is an anionic peptide that includes several phosphorylated forms. Phosphorylation has been shown to be important for anti-microbial activity. Because of the amino acid sequences of the peptides discussed in Reynolds, and the phosphorylation of certain amino acids, the peptides exhibit a net negative charge.

As a result of this net negative charge, a person skilled in the art would expect that combining the peptides discussed in Reynolds with zinc ions would lead to the formation of a complex. Because the zinc ion is positively charged, it would be expected to form an ionic complex with the negatively charged peptides. However, the teachings of Cummins that the anti-microbial effects of zinc are reduced by complexation teach away from making a composition comprising a peptide as discussed in Reynolds and a zinc ion. As such, Cummins teaches away from the Office Action's proposed modification of Reynolds.

The expectation of a person skilled in the art that a negatively charged peptide as discussed in Reynolds would form a complex with positively charged zinc ions has been empirically confirmed in the present application. Structural studies described in the instant application confirm that there are two binding sites for zinc in the peptide κ-casein-A (106-169). Similar results were also obtained for calcium binding (see, e.g., instant specification at page 19).

The September 1, 2010 U.S. Patent Office's examination guidelines ("Guidelines") on obviousness states:

> A claimed invention is likely to be obvious if it is a combination of known prior art elements that would reasonably have been expected to maintain their respective properties or functions after they have been combined.

The Guidelines cite in this connection *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356 (Fed. Cir. 2008). However, as noted above, the instant case does not involve "a combination of known prior art elements that would reasonably have been expected to maintain their respective properties or functions after they have been combined." Cummins's teaching that the anti-microbial effects of zinc are reduced by complexation indicate that zinc would not reasonably have been expected to maintain its anti-microbial function when combined with a peptide of Reynolds.

Furthermore, the Guidelines indicate that:

> A claimed combination of prior art elements may be nonobvious where the prior art teaches away from the claimed combination and the combination yields more than predictable results.

In this context, the Guidelines cite *Crocs, Inc. v. U.S. Int'l Trade Comm'n.*, 598 F.3d 1294 (Fed. Cir. 2010).

Furthermore, a claimed composition comprising a combination of a peptide as recited and a zinc ion exhibits **synergistic effects**. Specification, page 2, lines 15-17; page 19, lines 7-10; Table 2; and Figure 3. Thus, a claimed composition "yields more than predictable results"; and as such, according to the Guidelines, cannot be considered obvious over the cited art.

In summary, the cited art fails to provide motivation to combine the reference teachings or to make the proposed modification; Cummins teaches away from the proposed modification; and the combination of elements recited in claim 1 yields more than predictable results. For at least these reasons, Reynolds, alone or in combination with Cummins and Phan, cannot render any of claims 1-11 and 16-19 obvious.

Conclusion as to the rejection under 35 U.S.C. §103(a)

Applicants submit that the rejection of claims 1-11 and 16-19 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number FREE-004.

Respectfully submitted,
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Date: July 25, 2011

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